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(21) International Application Number: PCT/GB91/01960 (22) International Filing Date: 7 November 1991 (07.11.91) (30) Priority data: 9024365.0 9 November 1990 (09.11.90) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : TAYLOR, Anthony, James [GB/GB]; BURNELL, Patricia, Kwong, Phieu [GB/GB]; Glaxo Group Research Limited, Park Road, Ware, Hertfordshire SG12 0DG (GB).		(74) Agents: FILLER, Wendy, Anne et al.; Glaxo Holdings plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU+, TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i>
(54) Title: AEROSOL MEDICAMENTS (57) Abstract Aerosol formulations comprising: (A) a medicament in particulate form and having a surface coating of a surfactant; (B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant; and (C) a cosolvent having higher polarity than the propellant which cosolvent is present in an amount of up to 5 % w/w based upon propellant; and methods for their preparation.		

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Aerosol medicaments

This invention relates to aerosol formulations of use in the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol.

The most commonly used aerosol propellants for medicaments have been Freon 11 (CCl_3F) in admixture with Freon 12 (CCl_2F_2) and Freon 114 ($\text{CF}_2\text{Cl.CF}_2\text{Cl}$). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrogen-containing chlorofluorocarbons and fluorocarbons; medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777. EP 0372777 requires the use of 1,1,1,2-tetrafluoroethane in combination with both a cosolvent having greater polarity than 1,1,1,2-tetrafluoroethane (e.g. an alcohol or a lower alkane) and a surfactant in order to achieve a stable formulation of a medicament powder. In particular it is noted in the specification at page 3, line 7 that "it has been found that the use of Propellant 134a (1,1,1,2-tetrafluoroethane) and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers".

We have now surprisingly found that, in contradistinction to this teaching, it is in fact possible to obtain stable dispersions of finely-powdered medicaments together with surfactants in hydrogen-containing fluorocarbon or chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane if the surfactant is present as a dry coating on the particles of medicament and that the stability of the resulting dispersion is enhanced by the presence of small

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8. A formulation as claimed in any one of claims 1 to 7 wherein the surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate.
9. A formulation as claimed in any one of claims 1 to 8 wherein the surfactant-coated medicament is present in an amount of 0.005-5% w/w based upon the total weight of the medicament.
10. A formulation as claimed in any one of claims 1 to 9 wherein the medicament is selected from salbutamol, salmeterol, beclomethasone esters or fluticasone esters.
11. A method for the preparation of an aerosol formulation comprising dispersing a surface-coated medicament in a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant in an aerosol container and then adding the cosolvent.
12. A method as claimed in claim 11 wherein the surface-coated medicament is obtained by slurring particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01960

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
 Int.Cl.5 A 61 K 9/12 A 61 K 9/72

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation
 to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US,A,4352789 (C.G. THIEL) 5 October 1982, see the claims 1-5,11-13,15-17; column 5, lines 17-24; column 6, lines 8-15 ---	1-12
Y	EP,A,0372777 (RIKER) 13 June 1990, see the claims 1-2,5-6,10-13 (cited in the application) ---	1-12
P,Y	WO,A,9104011 (RIKER) 4 April 1991, see the claims -----	1-12

¹⁰ Special categories of cited documents:

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IV. CERTIFICATION

Date of the Actual Completion of the International Search 18-12-1991	Date of Mailing of this International Search Report - 9. 01. 92
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. PEIS <i>M. Peis</i>

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9101960
SA 53071

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/01/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4352789	05-10-82	None	
EP-A- 0372777	13-06-90	AU-A- 4595689	14-06-90
		CA-A- 2004598	06-06-90
		JP-A- 2200627	08-08-90
WO-A- 9104011	04-04-91	AU-A- 6409790	18-04-91

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